Requested Patent: WO9703672A1

Title: THERAPEUTIC USE OF D-THREO-METHYLPHENIDATE ;

Abstracted Patent: WO9703672 ;

Publication Date: 1997-02-06 ;

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Application Number: WO1996GB01689 19960715 ;

Priority Number(s): GB19950014416 19950714; GB19960005523 19960315 ;

IPC Classification: A61K31/445 ;

Equivalents:

AU6466096, AU702801, CA2223629, EP0839038 (WO9703672), JP11509227T ;

ABSTRACT:

A method for the treatment of a human patient having a condition susceptible to treatment with methylphenidate, and wherein the patient exhibits or is susceptible to hepatic dysfunction, comprises the administration of d-threo-methylphenidate.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 31/445 // (A61K 31/445, 31:00)

A1

(11) International Publication Number: WO 97/03672

(43) International Publication Date: 6 February 1997 (06.02.97)

(21) International Application Number: PCT/GB96/01689

(22) International Filing Date: 15 July 1996 (15.07.96)

(30) Priority Data:

9514416.8	14 July 1995 (14.07.95)	GB
9605523.1	15 March 1996 (15.03.96)	GB

(81) Designated States: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

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(54) Title: THERAPEUTIC USE OF d-threo-METHYLPHENIDATE

(57) Abstract

A method for the treatment of a human patient having a condition susceptible to treatment with methylphenidate, and wherein the patient exhibits or is susceptible to hepatic dysfunction, comprises the administration of *d-threo*-methylphenidate.

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THERAPEUTIC USE OF *d-threo*-METHYLPHENIDATE

Field of the Invention

This invention relates to new therapeutic uses of *d-threo*-methylphenidate (abbreviated herein as dtmp).

Background of the Invention

Methylphenidate is a known drug. It is used primarily to treat hyperactive children. It may have to be administered over a prolonged period of time, and is a controlled substance.

Methylphenidate is a chiral molecule. The properties of the enantiomers have been investigated to some extent, although the drug is still administered as the racemate. It is generaly thought that dtmp is the active material, and that its antipode (ltmp) is metabolised more rapidly.

Methylphenidate is often administered in a sustained-release formulation. For example, a coated tablet comprising racemic methylphenidate is administered, with a view to maintaining a therapeutically-effective level of the drug. This formulation does not always provide a reproducible or a sustained effect.

Roberts *et al*, Life Sci. 55:269-281 (1994), found that racemic methylphenidate caused hepatic dysfunction in the mouse, manifest as elevated liver enzyme levels and/or coagulative necrosis, on morphological investigation of the liver. Also, the National Toxicity Programme (NTP TR439) of the USA recently (1995) found that racemic methylphenidate caused, in the mouse, hepatocellular and centri-lobular hypertrophy, formation of foci of damaged cells and hepatic tumours.

Mehta *et al*, J. Clin. Gastroenterol. 6:149-151 (1984), report hepatic dysfunction due to intravenous abuse of methylphenidate hydrochloride. Goodman, New York State Journal of Medicine 72:2339-40 (15 September 1972), reports hepatoxicity due to methylphenidate hydrochloride. Stecyk *et al*, Annals of Emergency Medicine 14:597/113-599/115 (6 June 1985), report multiple organ failure resulting from intravenous abuse of methylphenidate hydrochloride.

Summary of the Invention

This invention is based on the discovery that dtmp can satisfactorily be used to treat human patients exhibiting or susceptible to hepatic dysfunction, or to reduce the likelihood of such symptoms occurring. dtmp may also be used instead of the racemate in therapy involving the use of other drugs that have effects likely to be exacerbated by use of the racemate. Such effects may include hepatic dysfunction. The patient may be an adult, e.g. in the treatment of compulsive shopping disorder or narcolepsy, or a child, e.g. a pre-pubertal child suffering from attention-deficit hyperactivity disorder (which, for the purposes of this specification, includes attention-deficit disorder).

The discovery is based on the finding that, in an animal model, dtmp is surprisingly less hepatotoxic than racemic methylphenidate.

Description of the Invention

The dtmp that is used in this invention is substantially free of ltmp, e.g. in an enantiomeric excess (ee) of at least 70%, preferably at least 90%, and more preferably at least 95%. The dtmp may be substantially enantiopure. It may be used in the form of any suitable salt, e.g. the hydrochloride.

The dtmp may be administered by the same means as is known for racemic methylphenidate, in a sustained-release formulation, e.g. a coated tablet. It may be administered in any other conventional sustained-release formulation, via any suitable route of administration. Conventional dosing parameters may be adopted, i.e. those which are known to or adapted to the practice of those skilled in the art. For example, the daily dosage of dtmp may be 5 to 60 mg, but will be chosen according to the age, weight and health of the subject, and other factors that are routinely considered by the man skilled in the art.

Other advantages of the use of dtmp may include the reduction of exposure to a controlled substance, reduced

side-effects (which include anorexia, insomnia, stomach ache and headache), reduced abuse potential, reduced C_{max}, a reduced level of active material even when chewed, reduced patient variability, reduced interaction with ltmp or other drugs, and less variability between fed and fasted subjects.

By controlling the nature of the formulation, it is possible to control dissolution *in vitro*, and thus match or exceed the US National Formulary (NF) drug release profile for methylphenidate hydrochloride. Further, when administered to a healthy subject, a serum level of dtmp can be attained that is at least 50% of C_{max}, over a period of at least 8 hours, e.g. 8-16, 8-12 or 8-10 hours. Thus, for example, a shorter release period may be preferred or a different period before the serum level drops below a different proportion of C_{max}.

The serum level may be also controlled so that it remains high during the day, after taking a dosage in the morning, and is reduced in the evening, before it can have any undesirable effect on sleeping patterns.

A formulation of the invention may be a unit dosage such as a tablet, capsule or suspension. A sustained-release formulation may be in matrix, coating, reservoir, osmotic, ion-exchange or density exchange form. It may comprise a soluble polymer coating which is dissolved or eroded, after administration. Alternatively, there may be an insoluble coating, e.g. of a polymer, through which the active ingredient permeates, as from a reservoir, diffuses, e.g. through a porous matrix, or undergoes osmotic exchange. A further option for a sustained-release formulation involves density exchange, e.g. in the case where the formulation alters on administration, e.g. from microparticles to a gel, so that the active ingredient diffuses or permeates out. Ion-based resins may also be used, the active component being released by ionic exchange, and wherein the rate of release can be controlled by using cationic or anionic forms of the drug.

It is preferred to use a formulation in this invention that is resistant to chewing, e.g. micronised particles that are individually coated and which do not immediately release the active component on chewing, or possibly even actively discourage chewing by their consistency. Many effects, benefits etc. described herein apply also to formulations providing immediate release. The various effects etc. may be due to the use of dtmp and/or the absence of ltmp.

Various circumstances may cause hepatic dysfunction, or render a patient susceptible to such a problem. Such circumstances include the administration of a therapeutic agent in which liver dysfunction, is a side-effect, or the taking of drugs of abuse known to cause liver dysfunction, e.g. alcohol or ecstasy.

Hepatic dysfunction may be evident in terms of interference with enzyme function, or changes in the levels of certain enzymes such as alanine aminotransferase (ALT), or in terms of gross alterations such as cirrhosis or cancer of the liver. Hepatic dysfunction can be determined by the skilled man, as may be susceptibility or predisposition to such dysfunction.

Methylphenidate-Induced Hepatotoxity in Mice

Experiments were carried out to investigate the differing toxicity effects of dtmp and racemic methylphenidate characterised by elevated liver enzyme levels and instances of coagulative necrosis in the liver. The procedures followed were as described in Roberts *et al*, *supra*.

Groups of 21 male mice of the Crl:CD-1(ICR)BR strain were given a single intraperitoneal dose of the compounds in a saline solution with an injection volume of 10 ml/kg body weight. The animals were housed in groups of three in polypropylene cages with a steel mesh floor in a single, exclusive room, air conditioned to provide a minimum of 15 air changes/hour. Animal quarters were temperature and humidity controlled with a 12 hour light/dark cycle.

Blood samples were obtained from all animals at 16 hours after dosing for determination of serum alanine aminotransferase (ALT) activity. The results are tabulated below.

Livers were removed 24 hours after dosing and preserved in fixative of 10% neutral buffered formalin for histopathological examination. The livers were embedded in paraffin wax, sectioned at a nominal 5 μm, stained with haematoxylin and eosin, and examined using light microscopy. The results are tabulated below.

Compound	Dose (mg/kg)	ALT Levels (IU/L)	Coagulant Necrosis
Control (water)	0	81	0
Racemate	75	185	2
dtmp	75	76	0

The results show that there is a marked beneficial effect of treatment with dtmp relative to treatment with racemic methylphenidate, in that plasma levels of the liver enzyme alanine aminotransferase were not increased. The histopathology data further support the finding that dtmp treatment has beneficial advantages over treatment with the racemate. Coagulant necrosis was detected in two animals out of 21 in the group receiving racemic methylphenidate, whereas there were no cases with dtmp. Thus, the results show a marked difference.

CLAIMS

1. A method for the treatment of a human patient having a condition susceptible to treatment with methylphenidate, and wherein the patient exhibits or is susceptible to hepatic dysfunction, which comprises the administration of *d-threo*-methylphenidate.

2. A method for the treatment of a human patient having a condition susceptible to treatment with methylphenidate, wherein the patient is or has been exposed to circumstances that cause, or render the patient susceptible to, hepatic dysfunction, which comprises the administration of *d-threo*-methylphenidate.

3. A method according to claim 1 or claim 2, wherein the patient has previously undergone, or is simultaneously undergoing, administration of a therapeutic agent that may cause or render the patient susceptible to hepatic dysfunction.

4. A method according to claim 3, wherein said therapeutic agent is racemic methylphenidate.

5. A method according to claim 1 or claim 2, wherein the patient has previously, or is simultaneously, taking a drug of abuse known to cause liver dysfunction or damage, including alcohol or ecstasy.

6. A method according to any preceding claim, wherein the patient has abnormal levels of at least one liver enzyme.

7. A method according to claim 6, wherein the at least one liver enzyme is CYP2D6 or another P_{450} cytochrome enzyme.

8. A method according to any preceding claim, wherein the condition is selected from depression, compulsive shopping disorder, narcolepsy, insomnia and attention-deficit hyperactivity disorder.

9. A product containing *d-threo*-methylphenidate and a therapeutic agent as defined in claim 3, as a combined preparation for simultaneous, separate or sequential use in the treatment of a condition as defined in claim 1 or claim

2 and a condition susceptible to treatment with said therapeutic agent.

INTERNATIONAL SEARCH REPORT

Inte. onal Application No
PCT/GB 96/01689

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/445 //(A61K31/445,A61K31:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CLINICAL PHARMACOLOGY AND THERAPEUTICS, vol. 55, no. 3, March 1993, USA, XP000602459 AOYAMA ET AL: "PHARMACOKINETICS OF (+)-THREO-METHYLPHENIDATE ENANTIOMER IN PATIENTS WITH HYPERSOMNIA" see page 272, right-hand column, line 1-27 ---	1-9
Y	MOLECULAR PHARMACOLOGY, vol. 40, no. 1, July 1991, USA, pages 63-68, XP000602574 TYNDALE ET AL: "NEURONAL CYTOCHROME P450IID1 (DEBRISOQUINE/SPARTEINE-TYPE): POTENT INHIBITION OF ACTIVITY BY (-)-COCAINE AND NUCLEOTIDE SEQUENCE INDENTITY TO HUMAN HEPATIC P450 GENE CYP2D6." see page 65, right-hand column, line 29-30 --- -/--	6,7

[X] Further documents are listed in the continuation of box C. [ ] Patent family members are listed in annex.

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27 September 1996	29. 10. 96
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Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	J. PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 241, no. 1, April 1987, USA, pages 152-158, XP000602559 PATRICK ET AL : "PHARMACOLOGY OF THE ENANTIOMERS OF THREO-METHYLPHENIDATE" see abstract ---	1-9
Y	PHARMACOLOGY, BIOCHEMISTRY AND BEHAVIOR, vol. 40, no. 4, December 1991, USA, pages 875-880, XP000602558 ECKERMANN ET AL: "ENANTIOSELECTIVE BEHAVIORAL EFFECTS OF THREO-METHYLPHENIDATE IN RATS" see page 879, left-hand column, paragraph 2 - right-hand column, paragraph 5 -----	1-9